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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(54) Title: COMPOSITION FOR DELIVERY OF ORALLY ADMINISTERED SUBSTANCES</p> <p>(57) Abstract</p> <p>A composition comprised of non-esterified fatty acids having 14-18 carbon atoms; monoglycerides which are monoesters of glycerol and fatty acids having 14-18 carbon atoms; lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms and a drug. The composition is useful for the delivery of orally-administered drugs. The composition is also useful as a source of readily absorbable fat. When used in this manner, the composition is comprised of non-esterified fatty acids having 14-18 carbon atoms; monoglycerides which are monoesters of glycerol and a fatty acid having 14-18 carbon atoms; lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms. A method of making the compositions disclosed is also described.</p>		

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COMPOSITION FOR DELIVERY OF ORALLY  
ADMINISTERED SUBSTANCES

Description

Technical Field

- 5           This invention is in the field of biology and in particular relates to lipid compositions for the delivery and release of drugs and other substances via the lymphatics into the systemic circulation.

Background Art

- 10           Drug Absorption

- Drugs must reach their targets selectively and controllably if their desired pharmacological activities are to be maximized. One approach to optimizing the activities of drugs is their controlled and sustained delivery into the systemic  
15           circulation. Orally administered drugs are generally absorbed in the intestine. Such drugs undergo first pass clearance by the liver and small intestine; that is, they are converted by the intestine  
20           and the liver to pharmacologically inactive metabolites and/or are secreted into bile by the liver, either as drug or as active metabolites. As a result, the amount of an orally administered drug

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actually entering the systemic circulation can be much less than the amount administered. To ensure that effective quantities of such a drug will enter the circulation and reach the targeted site(s) in the body, larger quantities than actually needed must be administered and often must be given in several smaller doses, rather than one dose. Orally administered drugs also typically have poor bio-availability. For example, they may be adversely affected by the pH and the enzymatic activity of the stomach and intestine and may be poorly dissolved in the stomach and intestinal fluids.

There have been numerous attempts to address these problems and to improve the bioavailability of orally administered drugs. The efficacy of some drugs given orally has been improved by administering them with a triglyceride or neutral fat. Such fats represent an environment that is compatible with lipophilic drugs, i.e. they exhibit low aqueous solubility. Fats also enhance the stability of drugs which are unstable in the stomach and intestine. The end products of fat digestion are absorbed by the villi of the intestinal mucosa into a lymphatic vessel, the central lacteal; absorption occurs within a region of the intestine in which limited drug metabolism occurs. The absorbed fat is transported through the thoracic duct, the major lymphatic channel and is subsequently emptied into the blood; it is not carried in the portal blood, which goes to the liver, where first pass metabolism of drugs occurs.

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The absorption of griseofulvin has been shown to be enhanced if the drug is co-administered with a high fat content meal or in an oil and water emulsion. Crounse, R.G., Journal of Investigative Dermatology, 37:529 (1961); Carrigan, P.J. and Bates, T.R., Journal of Pharmacological Science, 62:1476 (1973). If the hormone testosterone undecanoate is administered in a peanut oil solution, it is more biologically active than if it is administered in an aqueous micro-crystalline suspension. Coert, A. J. et al., Acta Endocrinol, 79: 789, (1975); Hirschhauser, C. et al., Acta Endocrinol., 80:179. (1975). This effect is presumed to be due to absorption of the steroid via the thoracic lymph rather than the portal blood; in this way, first pass clearance by the liver is avoided.

Cholesterol, its esters and triglyceride constituents (e.g., fatty acids and monoglycerides) are absorbed via the thoracic lymph. The effects of some of these compounds, alone or in the presence of bile salts, upon absorption of some orally administered drugs have been evaluated. For example, oral administration of ubidecarenone, which is used for treating hypertension, in a mixture containing fatty acids having 12 to 18 carbon atoms and monoglycerides containing such fatty acids, resulted in somewhat greater absorption of the ubidecarenone than occurred after oral administration of the drug alone (8.3% v. 2.3%). Taki, K. and Takahira, H., U.S. Patent 4,325,942. (1982). If the steroid progesterone is administered orally in combination

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with cholesterol or its esters, good sustained biological activity can be obtained. This is believed to be due to the absorption of progesterone via the thoracic lymph and not via the portal  
5      circulation. Kincl, F. A., Proceedings of the 6th International Congress of Pharmacology, 5:105, (1975).

Yesair has evaluated the effect of fatty acids having 12 to 18 carbon atoms, monoglycerides of  
10    these fatty acids, and bile salts on the absorption of orally administered estradiol, which is an estrogenic hormone. Yesair, D. W., PCT WO 83/00294 (1983). The mole ratio of fatty acids: monoglycer-  
15    ides: bile salts evaluated ranged from 10:1:1, 1:1:10 or 1:10:1. The preferred ratio is stated to be 2:1:2, which is similar to the micellar composition resulting from the enzymatic digestion of triglycerides in the intestine, which occurs in the presence of bile salts and calcium ions. When  
20    excess bile salts are present, estradiol incorporated into the 2:1:2 composition can migrate or partition into a bile salt-enriched micellar solution. This migration or partitioning of estradiol occurred prior to absorption of the drug, as shown  
25    by the fact that the initial concentrations in plasma of estradiol are initially greater than those in lymph. In addition, about 25-50% of the estradiol administered in the composition was co-absorbed with the lipid constituents and entered  
30    the systemic circulation via the thoracic lymph.

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The presence of bile salts, which are absorbed in the ileum (and not in the jejunum, as is most fat) compromised the co-absorption of estradiol with fat by enhancing the migration of the drug from fat to the bile salt micelle. Phosphatidyl choline was used in an effort to maintain the estradiol within the micellar composition in which fatty acids:- monoglycerides:bile salts occurred in a 2:1:2 molar ratio. In the presence of excess bile salts, about 60% of the estradiol incorporated into the 2:1:2 micellar composition remained associated with it when phosphatidyl choline was not present. Under the same conditions, about 70-75% of the estradiol remained in the composition when phosphatidyl choline was used. Addition of phosphatidyl choline for this purpose, however, results in an increased size of the delivery system. Size is an important parameter in the absorption of lipid micelles and this effect of phosphatidyl choline might interfere with co-absorption of the drug with the lipids. In addition, excess phosphatidyl choline has been shown to reduce lipid absorption. Ammon, H. V. et al., Lipids, 14:395 (1979); Clark, S. B., Gastrointestinal Physiology, 4: E183 (1978).

Others have also described the effects of the presence of bile salts in lipid formulations used for co-absorption of drugs. Wilson, T. H., In: Intestinal Absorption, Saunders, (1962); Lack, L. and Weiner, I.M., American Journal of Physiology, 240:313, (1961); H. V. Ammon et al, Lipids, 14: 395, (1979). For example, little difference in the



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absorption of 5-fluorouracil (5FU) in the stomach or small intestine was evident when the 5FU was administered alone or in a mono-olein/sodium taurocholate mixed micelle formulation. 5FU absorption in the large intestine was greater when the drug was administered in the formulation than when it was administered alone. Streptomycin is poorly absorbed from the intestine. Muranushi and co-workers report that mixed micelles, composed of bile salts, mono-olein or unsaturated fatty acids, did not improve the absorption of streptomycin from the small intestine but markedly enhanced the absorption from the large intestine. The enhancement in the large intestine was attributed mostly to the alteration of the mucosal membrane permeability by mono-olein or unsaturated fatty acids. In contrast, mixed micelles of bile salts and saturated fatty acids produced only a small enhancement in streptomycin absorption even from the large intestine.

Muranushi, N. et al., Journal of Pharmaceutics, 4: 271 (1980). Taniguchi et al. report that mono-olein/taurocholate or oleic acid/taurocholate promotes the absorption of heparin, which is poorly absorbed when administered alone. Taniguchi, K. et al., International Journal of Pharmaceutics, 4:219 (1980). Absorption of heparin from the large intestine was twice that which occurred from the small intestine. The concentration of heparin in the mixed micelle to produce the potentiation in the large intestine was approximately one-fourth that required in the small intestine.

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In U. S. Patent 4,156,719, Sezoshi and Muranishi describe a micelle solution for rectal administration of water-soluble drugs that are poorly absorbed. The composition consists of fatty acids having 6-18 carbons, and/or mono- or di-glycerides having the same type of fatty acids; a bile salt or other non-ionic surface active agent; and water. A lysophosphatidyl choline moiety can be substituted for the fatty acids and mono- or di-glycerides. Absorption of streptomycin and gentamycin from the rectum and large intestine is reported to be comparable when the drug is administered in a bile salt: mixed lipid micelle. Similar formulations were not effective in increasing absorption in the duodenum. Muranushi, S. et al., International Journal of Pharmaceutics, 2:101 (1979). Absorption of the two drugs via the rectum and large intestine was markedly greater than that of a comparable dose administered duodenally, even when the mixed lipid micelle concentration administered duodenally was four times that administered via the other routes.

At the present time, there is a need for a more effective method of enhancing absorption of orally administered drugs from the small intestine. Much of a drug administered orally never reaches the targeted sites, either because the drug is poorly absorbed or because after it is absorbed, much is removed by the liver. If a more effective means were available to enhance the absorption of a drug, therapy would be more efficient because a smaller

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quantity of the drug would need to be administered to ensure that the desired amount would reach the target sites.

#### Nutrition

5           The caloric requirements of individuals are primarily a function of body composition and level of physical activity. Medically compromised, aged and physically stressed individuals often have limited body fat. Consequently, energy (caloric)  
10 needs will be satisfied mainly from exogenous sources.

Physical activity uses muscle and the energy requirements of all muscles, including the heart, are met primarily as a result of oxidation of fatty  
15 acids, from dietary fat or mobilized adipose fat. Adipose fat can, as noted, be minimal and therefore efficient absorption of fat can be an important consideration in satisfying the energy demands of the medically infirm, the aged and the physically  
20 active.

Fat absorption can be compromised in many circumstances. For example, in cystic fibrosis, a disorder of exocrine glands, there is a deficiency of pancreatic enzymes, bile salts and bicarbonate  
25 ions. Nutrition Reviews, 42: 344 (1984); Ross, C. A., Archives of Diseases of Childhood, 30: 316 (1955); Scow, R. O. E., Journal of Clinical Investigation, 55: 908 (1975). Fat absorption in cystic fibrosis patients can be severely affected  
30 and 30 to 60 percent of ingested fat can be malabsorbed. The malabsorption and resulting

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steatorrhea are generally not successfully handled by the oral administration of pancreatic lipase. In an effort to control the steatorrhea, the patient may consume less fat than desirable for good health.

5        Fat absorption can be compromised under stressful conditions and the generally accepted way of addressing this problem has been to reduce fat consumption. This approach can result in both acute and chronic medical problems. These problems might  
10       be avoided, or at least minimized, if a readily absorbable source of fat could be made available.

#### Disclosure of the Invention

      The subject of this invention is a composition comprised of: 1) non-esterified fatty acids having  
15       14-18 carbon atoms, 2) monoglycerides which are monoesters of glycerol and fatty acids having 14-18 carbon atoms, 3) lysophosphatidyl choline in which the fatty acid component has 14-18 carbon atoms, and  
20       4) a drug. The non-esterified fatty acids and the esterified fatty acid moieties of the monoglycerides and the lysophosphatidyl choline can be unsaturated or saturated. In particular, the unsaturated fatty acids can be palmitoleic, oleic, linoleic or  
25       linolenic, which can be present in the composition individually or in combination. The saturated fatty acids, which also have 14-18 carbon atoms, can be, for example, myristic, palmitic or stearic.

      The non-esterified fatty acids and the monoglycerides are present in the composition in a molar  
30       ratio of between about 2:1 and about 1:2 (non-

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esterified fatty acids:monoglycerides). The lyso-phosphatidyl choline comprises from about 1.0 mole % to about 30.0 mole % of the total composition.

5 If the non-esterified fatty acids in the composition are saturated, sufficient quantities of divalent cations (approximately one-half the molar amount of the fatty acids), such as calcium ions, are added to form non-esterified fatty acid salts.

10 The composition of this invention is designed to promote uptake of the mixed lipid colloid into the mucosa of the small intestine, subsequent synthesis into chylomicrons, translocation of the chylomicrons to the thoracic lymph and transport to the systemic circulation (i.e., blood).

15 The composition which is the subject of this invention will promote rapid and quantitative absorption of lipids in the small intestine and transport of lipids via the lymphatics because of several characteristics. First, the mole ratio  
20 described for the fatty acids and monoglycerides is optimal for their absorption in the jejunum. Second, the unsaturated fatty acids or saturated fatty acid-calcium salts included in the composition have been shown to be maximally absorbed and prefer-  
25 entially transported via the thoracic lymph (and not transported via the portal blood). Third, the composition also contains lysophosphatidyl choline, which enhances translocation of the reconstituted lipids as chylomicrons into the thoracic lymph.

30 The composition which is the subject of this invention can serve as a vehicle for enhanced uptake

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and bioavailability of drugs. Drugs are broadly defined here as any chemical agents or chemical substances which affect living processes. Examples of substances which can be incorporated into the composition of this invention are drugs administered for diagnostic, therapeutic or preventive purposes; lipophilic pro-drugs; bioactive peptides; some nutrients, such as fat-soluble vitamins, and other xenobiotics. This enhancement occurs because the substance incorporated into the composition of this invention is absorbed along with the lipids and subsequently enters the systemic circulation via the lymphatics. As a result, it is absorbed more rapidly and more completely than it otherwise would be. Because first pass clearance by the liver is avoided, more of the absorbed dose enters the blood and is available to reach target sites than would be available if the lipid formulation were not used.

The subject composition can also serve as a highly concentrated source of readily absorbable fat, which can be used, for example, by those in need of a calorically dense dietary component. When used in this manner, the composition of the present invention is comprised of 1), 2) and 3) as described above and does not include a drug.

The subject composition also provides a stable mixed lipid colloid that will protect the drugs from, for example, enzymatic and chemical degradation in the stomach and upper intestine. In addition, the inherent stability of the lipid components will make the compositions stable over extended

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periods and thus can serve as stable delivery vehicles for the substances incorporated into the formulation.

#### Brief Description of the Drawings

- 5        Figure 1 is a graph showing the total vitamin A-derived radioactivity equivalents over time in plasma of rats given  $^3\text{H}$ -vitamin A in a composition and in plasma of rats given  $^3\text{H}$ -vitamin A in corn oil.
- 10       Figure 2 is a graph showing the mean plasma concentration-time profiles of N-(4-Hydroxyphenyl)-all-trans-retinamide (HPR) in dogs following oral administration of HPR.

#### Best Mode of Carrying Out the Invention

- 15       The composition of the present invention, which is comprised of non-esterified fatty acids, mono-glycerides of those fatty acids, lysophosphatidyl choline having those fatty acids as their fatty acid moiety, and a drug is based on the absorption and
- 20       transport characteristics of the fatty acids and the contribution of lysophosphatidyl choline to solubilization of the drug in the lipid composition and to translocation of absorbed fat into the lymph (rather than into the portal circulation).
- 25       Hydrolysis of triglycerides yields a molar ratio of fatty acids to monoglyceride of 2:1. In subsequent absorption and resynthesis in the intestinal muscosa, dietary fatty acids are mixed and

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lose their identity; new triglycerides, partly characteristic of the species, are formed.

Two constituents of bile are fatty acids and phosphatidyl choline. Enzymatic hydrolysis of phosphatidyl choline yields fatty acids; complete hydrolysis produces two molecules of fatty acid and partial hydrolysis produces one molecule of fatty acid and lysophosphatidyl choline. As a result, a composition having an excess of monoglyceride (e.g., fatty acid:monoglyceride ratio of 1:2) can equilibrate with those fatty acids derived from bile to approximate the optimum ratio of 2:1 for the enhanced absorption of mixed lipid colloids from the upper intestine. A ratio of fatty acid:monoglycerides which is not within this range (i.e., 1:2 to 2:1) may not enhance lipid absorption. It may also compromise not only lipid absorption, but also co-absorption of drugs administered with the lipids. A less effective means of accommodating the excess fatty acids is the addition of glycerol in place of monoglycerides. If the component lipids are not absorbed within the jejunal region of the intestine, they progress along the small intestine to the large intestine. The drugs which migrate with the lipids may be absorbed and transported via the portal blood for first pass clearance by the liver. Once in the large intestine, the component lipids are utilized by the intestinal microflora. These microorganisms may also metabolize the drug co-migrating with the component lipids to produce toxicologically-active species. Goldman, P. In: The Molecular and Cellular



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Approaches to Understanding the Mechanisms of  
Toxicity, A.H. Tashjian (ed.) 164, (1983).

Absorption of saturated fatty acids has been shown to be inversely related to the number of carbon atoms in the fatty acid. For example, absorption of decanoic (10:0, which denotes chain length and degree of unsaturation) is almost quantitative. For lauric (12:0), it is more than 95%; for myristic (14:0), 80-90%; for palmitic (16:0), 65-70% and for stearic (18:0), 30-45%.

Transport of absorbed fatty acids via the lymph (and not in the portal circulation) varies greatly. That is, a much larger percentage of absorbed unsaturated fatty acids has been shown to be carried in the lymph than is the case for saturated fatty acids. About 85% of unsaturated fatty acids has been shown to be carried in the lymph. Miura, S. et al., Keio Journal of Medicine, 28: 121 (1979). In contrast, 5-20% of absorbed decanoic (10:0) and 15-55% of absorbed lauric (12:0) is transported in the lymph, even though 95% of a given quantity of each will be absorbed. The remainder is absorbed into the portal blood. As noted above, the percent absorption of saturated fatty acids is inversely related to chain length. That is, myristic (14:0) is absorbed to a greater extent than is palmitic (16:0), which in turn is absorbed to a greater extent than is stearic (18:0). The amount of these absorbed fatty acids being carried in the lymph is also inversely related to chain length: 68-80% for myristic; 85% for palmitic and stearic. In addition,

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unsaturated fatty acids (e.g., linoleic 18:2) have been shown to be absorbed into lymph more rapidly and to a greater extent than are saturated fatty acids. Taniquchi, K., International Journal of Pharmaceutics, 4: 219 (1980).

If saturated fatty acids are included in the composition of this invention, they are included as calcium salts or salts of another cation. This is true because the enzymatic hydrolysis of triglycerides, which releases saturated fatty acids, favors their calcium soap formation. Tak, Y. A. and Grigor, M. R., Biochimica Biophysica Acta, 531: 257 (1978).

Translocation of absorbed fat into the lymph has been shown to require lysophosphatidyl choline. Lysophosphatidyl choline and phosphatidyl choline both contain phosphoryl choline linked to C-1 of glycerol, but differ in the number of fatty acids they contain. Lysophosphatidyl choline has a single fatty acid component located at either C-1 or C-2 of the molecule; phosphatidyl choline has two fatty acid moieties (one at C-1 and one at C-2). The rate, but not the magnitude, of the translocation of absorbed fat is apparently related to the fatty acid moiety of the lysophosphatidyl choline. For example, oleoyl lysophosphatidyl choline (derived from di-oleoyl phosphatidyl choline) results in a 100% increase in triglyceride and phospholipid in lymphatic transported fat when compared with the effects of a lysophosphatidyl choline derived from a phosphatidyl choline composed

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mainly of saturated fatty acids (e.g., palmitic, C16:0; stearic, C18:0). In the absence of luminal phosphatidyl choline to yield a lysophosphatidyl choline, there is an increased accumulation of mucosal triglyceride and apparently increased portal transport of the absorbed fatty acids. Tso, P et al., Gastroenterology, 80: 60 (1981); O'Doherty, P.J.A. et al., Lipids, 8:249 (1973). If the fat load is increased five fold, a deficiency in lymphatic transport of absorbed fat becomes apparent. This effect is remedied by the addition of a source of lysophosphatidyl choline. Tso, P. et al., Gastroenterology, 73: 1362 (1977). This effect by lysophosphatidyl choline which is observed in vivo is also apparent in vitro. Rodgers, J. B., and O'Connor, P. J., Biochimica Biophysica Acta, 409:192 (1975). It has been shown that lysophosphatidyl choline is rapidly absorbed intact. Rodgers, J.B. et al., Digestive Diseases, 20:208 (1975); Nilsson, A., Biochimica Biophysica Acta, 137:240, (1976). Lymphatic phospholipids have also been shown to contain mainly unsaturated fatty acids: oleic (18:1), 50 to 63%; linoleic (18:2), 17 to 20%; and arachidonic (20:4), 2 to 4%.

Incorporating an unsaturated lysophosphatidyl choline into the composition of this invention will enhance the translocation of the absorbed lipids and the co-absorbed drugs or other substances. In addition, lysophosphatidyl choline plays a role in the solubilization of some drugs (i.e., its presence

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enhances the solubility of the drugs in the composition).

The composition of this invention is comprised of non-esterified fatty acids having 14-18 carbon atoms; monoglycerides which are monoesters of glycerol and fatty acids having 14-18 carbon atoms; lysophosphatidyl choline in which the fatty acid moiety also has 14-18 carbon atoms, and a drug. The non-esterified fatty acids and the fatty acids of the monoglycerides and the lysophosphatidyl choline can be unsaturated or saturated and preferably will be unsaturated. Examples of unsaturated fatty acids which can be used in the composition of this invention are:

15	palmitoleic	$C_{16}H_{30}O_2$	16:1
	oleic	$C_{18}H_{34}O_2$	18:1
	linoleic	$C_{18}H_{32}O_2$	18:2
	linolenic	$C_{18}H_{30}O_2$	18:3

Examples of saturated fatty acids which can be used in the subject composition are:

20	myristic	$C_{14}H_{28}O_2$	14:0
	palmitic	$C_{16}H_{32}O_2$	16:0
	stearic	$C_{18}H_{36}O_2$	18:0

The non-esterified fatty acids and monoglycerides are present in amounts which result in a molar ratio of from about 2:1 to about 1:2 (non-esterified fatty acid:monoglyceride).

In addition, the composition has lysophosphatidyl choline, the fatty acid moiety of which has 14-18 carbon atoms and is preferably unsaturated. The fatty acid constituent of the lysophosphatidyl

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choline is preferably one of those listed above. The quantity of lysophosphatidyl choline in the composition is determined by the amount needed for enhanced solubilization of a drug to be administered  
5 in the composition and the amount needed for its role in translocation. In general, lysophosphatidyl choline comprises from about 1.0 mole % to about 30.0 mole % of the total composition. The fatty acids which comprise the composition of this inven-  
10 tion - whether as non-esterified fatty acids or as constituents of monoglycerides or lysophosphatidyl choline - can all be the same or a number of different ones can be included.

The composition of the present invention also  
15 comprises a drug, which can be any chemical agent or chemical substance which affects living processes. They include, but are not limited to drugs administered for diagnostic, therapeutic or preventive purposes; lipophilic pro-drugs; some nutrients, such  
20 as fat soluble vitamins, and other xenobiotics.

The composition of this invention is made according to the following method. The component lipids are weighed and mixed, with or without heat, to attain liquid homogeneity. The drug is added and  
25 dissolved, with or without heat, in the lipid mixture. A uniform state is indicated by the absence of any solids at the appropriate temperature for the mixture to be a liquid and the absence of any schleirin. A schleiric effect will be more  
30 apparent at greater concentrations of the drug in the lipid mixture. The formulation is stable to

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several freeze-thaw cycles; the appearance of solids or schleirin may indicate instability of the formulation.

5 A second method of making the formulation involves dissolving the component lipids and drug in a solvent or mixture of solvents and mixing to attain homogeneity. The solvents are removed, in vacuo or by other suitable methods. The criteria for a suitable formulation will be the same as noted  
10 above.

The composition of this invention is illustrated by the following examples.

#### EXAMPLE I

##### PREPARATION OF COMPOSITION AND COMPARISON

15 WITH CORN OIL AS A DELIVERY MEANS

#### Lipid Composition

Tritium labeled ( $^3\text{H}$ ) vitamin A (7 mg or 0.25 millimoles; 30 curies per mole; specific activity 1.26 mC/mmole; Hoffman LaRoche) was incorporated  
20 into a lipid formulation of the following composition: 56 mg. of oleic acid (NuCheck Prep, Inc.); 36 mg. of mono-olein (NuCheck Prep, Inc.) and 6 mg. of lysophosphatidyl choline derived from soy lecithin (A. E. Staley Mfg. Co.). This corresponds to an  
25 approximate molar ratio of oleic acid: mono-olein: lysophosphatidyl choline of 2:1:0.1. (The approximate molar percentages of the components were 64.5:32.3:3.2, respectively). The composition was administered to Sprague-Dawley rats (weighing  
30 210-230 gm) by gavage.

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Corn Oil Preparation

Tritium-labeled vitamin A (7mg. or 0.25 millimoles) was administered to Sprague-Dawley rats (as above) in 99 mg. food grade, refined corn oil (A. E. Staley Mfg. Co.).

Experimental Procedure and Results

The concentration of vitamin A equivalents in the plasma was measured by obtaining duplicate 0.05ml. blood samples from the orbital sinus at 0.5, 1, 2, 3, 4, 6, 8 and 24 hours after administration. The blood was collected in hematocrit tubes and centrifuged; the plasma was transferred into tared scintillation vials and weighed. The radioactivity was determined by liquid scintillation counting.

Results indicated a slow absorption of the vitamin A over an 8 hour period (Figure 1). An estimate of the amount that was absorbed as a function of time is shown in Table 1. About 73% of the vitamin A in the composition was absorbed within 2 hours after administration; approximately 50% of the vitamin A administered in corn oil was absorbed in the first 2 hours. At 3 hours after administration, more than 90% of the vitamin A in the lipid composition and 77% of that in the corn oil had been absorbed.

At the end of the 8-hour study period, absorption of vitamin A in both the composition and the corn oil was complete. The plasma concentration of tritiated vitamin A equivalents in rats in the two groups were comparable. The composition enhanced

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absorption of the vitamin A incorporated into it and also caused the vitamin to be absorbed more quickly.

5       The areas under the concentration-time curve for the 8 hour period were also equivalent, indicating that the absorption of vitamin A in the composition was quantitative. In a similar comparison, some 73% of the vitamin A in the composition was absorbed within 2 hours (Table 1) and was greater than 90% at 3 hours as compared to 52 and 77% for  
10   vitamin A, administered in corn oil. Thus it is apparent that the composition will provide for both the enhanced and earlier absorption of incorporated drugs and, therefore, enhance their effectiveness.



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Table 1: Percent Absorption of Vitamin A Adminis-  
tered in the Composition or in Corn Oil  
to Rats by Oral Intubation

5	<u>Hours</u>	<u>Percent Absorption</u>		<u>Ratio</u>
		<u>Lipid Composition</u>	<u>Corn Oil</u>	<u>Composition/Oil</u>
	0 - 0.5	5.4	4.0	1.35
	0.5 - 1	27.3	20.0	1.37
	1 - 2	72.6	52.4	1.39
	2 - 3	92.0	77.2	1.19
10	3 - 4	97.3	91.8	1.06
	4 - 6	100.	99.5	1.01
	6 - 8	100.	100.	1.00

#### EXAMPLE II

#### ESTIMATION OF CAPACITY AND STABILITY OF A COMPOSITION AS A VITAMIN A DELIVERY MEANS

A composition that included oleic acid, mono-glyceride and lysophosphatidyl choline as described in Example I was used for characterizing the capacity of the composition for vitamin A (also as described above). Vitamin A was added in batches to the composition as follows: 1st addition, 0.277 mmols; 2nd, 0.241; 3rd, 0.276; 4th, 0.262 and 5th, 0.285. The 5th addition resulted in the addition of 1.34 mmols or 384 mg of vitamin A to approximately 1 gm of the composition. The millimole ratio of the composition was approximately 2:1:0.1 (oleic acid: mono-olein:lysophosphatidyl choline).

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After each addition the approximate amount of time necessary for the complete dissolution of the added vitamin A was recorded, as was the extent of schlierin evident. The time needed to obtain a minimal schlieric effect was generally between 5 minutes and 60 minutes and inversely related to the amount of vitamin A added. After each addition and the achievement of a minimal schlieric effect, the solution was placed in an ice-bath in order to evaluate its stability. The relative viscosity of the cold solution was also recorded. These findings are summarized in Table 2.

A clear solution, without schleirin, was observed within an hour after the 5th addition. The same solution was frozen for one week and thawed. A clear solution was observed at that time. This freeze-thaw cycling was repeated four times over an 8-week period with comparable results. Thus it is apparent that this lipid formulation is stable over extended periods of storage and changes in temperature.

Table 2: The Capacity of the Composition  
for Vitamin A

25	<u>Vitamin A</u>		<u>Condition to Attain A Clear Solution</u>			
	<u>Added</u>	<u>Total</u>	<u>Time</u>	<u>Temp.</u>	<u>Schleirin</u>	<u>Viscosity</u>
	( <u>mmoles</u> )	( <u>mmoles</u> )				
	0.277	0.277	1 min.	20°C	none	normal
	0.241	0.518	1 min.	20°C	minimal	normal
	0.276	0.794	5 min.	37°C	medium	thicker
30	0.262	1.056	10 min.	37°C	medium	viscous
	0.285	1.341	10 min.	46°C	extensive	very viscous

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EXAMPLE III  
ESTIMATION OF SOLUBILITY OF  
N-(4-HYDROXYPHENYL)-ALL-TRANS-RETINAMIDE (HPR)  
IN LIPID FORMULATIONS

5    Lipid Formulations

          N-(4-Hydroxyphenyl)-all-trans-retinamide (HPR)  
          (McNeil Pharamceutical) was used for characterizing  
          its solubility in several formulations of the  
          composition of the present invention. The make up  
10    of the composition varied with respect to the fatty  
          acid constituents among the three basic components:  
          fatty acid (NuCheck Prep Inc.), monoglyceride  
          (NuCheck Prep Inc.), and lysophosphatidyl choline  
          (Avanti Polar Lipids). The formulations used are  
15    listed in Table 3.

          In each formulation, the lipid components were  
          first mixed together in a sealed container under  
          nitrogen. Solid HPR was added in increments. After  
          each addition, the container was resealed under  
20    nitrogen and heated and sonicated to produce a  
          solution of the HPR or until it became apparent that  
          the solid HPR would remain in suspension. Those  
          formulations which resulted in solution of HPR were  
          refrigerated or frozen and the continued solubili-  
25    zation of the HPR was noted. In all instances, the  
          HPR, once solubilized, did not precipitate out of  
          the solution.

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The results of observations for the formulations are shown in Table 3. In formulations II and III, solution of HPR was noted when the molar ratio of the lysophosphatidyl choline (LysoPC) to HPR  
5 (LysoPC:HPR) was greater than unity; a suspension of HPR was observed when the molar ratio of lysophosphatidyl choline to HPR was less than unity. In comparing formulations III and IV, which contained approximately the same amount of HPR, the LysoPC:HPR  
10 ratio was less than unity in formulation III when a suspension of HPR was observed and greater than unity in formulation IV when a solution was apparent. Comparison of formulations V and VI showed that the solution of HPR was apparent at molar ratio  
15 of 1 (LysoPC:HPR) for the lysophosphatidyl choline containing either the fatty acid myristoyl (14:0) or palmitoyl (16:0). In formulation V, the solubilization of the third sequential addition of HPR appeared to be more difficult than the first two  
20 additions. This is a further indication of the importance of having a molar ratio of LysoPC:HPR greater than 1.

Formulation VII represented a formulation of HPR that contained all the components of the previous formulations. As described in Example IV, it  
25 was administered to dogs. Briefly, the ratio of 18:1 LysoPC:HPR was 0.69; the ratio of 14:0 LysoPC:HPR was 0.33; and the ratio of 16:0 LysoPC:HPR was also 0.33. The molar ratio of lysophosphatidyl  
30 choline:HPR in Formulation VII was 1.31:1.

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Table 3: Solubility of HPR in Lipid Formulations

Formulation Number	Constituent	Lipid Formulation		Sequence Number	Addition of HPR		Sequential Observation After HPR Addition
		mg	mmoles		mg	mmoles	
II	18:1 FA	667	2.364	1.	10.3	0.026	1. Solution
	18:1 MG	358	1.004	2.	30.6	0.104	2. Suspension
	14:0 LysoPC	49	0.096				
III	18:1 FA	575	2.038	1.	22.1	0.056	1. Solution
	18:1 MG	356	0.9997	2.	35.7	0.147	2. Suspension
	18:1 LysoPC	92	0.0998				
IV	18:1 FA	473	1.680	1.	32.2	0.082	1. Solution
	18:1 MG	303	0.850	2.	37.9	0.179	2. Solution
	18:1 LysoPC	144	0.277				
V	18:1 FA	476	1.689	1.	51.9	0.132	1. Solution
	18:1 MG	300	0.844	2.	20.8	0.186	2. Solution
	14:0 LysoPC	128	0.278	3.	30.3	0.263	3. Solution
VI	18:1 FA	568	2.015	1.	73.1	0.187	1. Solution
	16:0 MG	333	1.007	2.	51.3	0.318	2. Solution
	16:1 LysoPC	160	0.318				
VII	18:1 FA		25.720	1.	16.004	4.087	1. Solution
	18:1 MG		9.594				
	16:0 MG		3.198				
			12.792				
	18:1 LysoPC		2.806				
	14:0 LysoPC		1.279				
	16:0 LysoPC		1.271				
			5.356				

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EXAMPLE IVBIOAVAILABILITY OF N-(4-HYDROXYPHENYL)-ALL-TRANS  
RETINAMIDE (HPR) ADMINISTERED IN A FORMULATION

The study was designed to compare the bioavailability of HPR from the lipid formulation VII (see Example III and Table 3), administered to beagle dogs under fasting (Treatment E<sub>1</sub>) and fed (Treatment E<sub>2</sub>) conditions with the bioavailability of HPR administered to Beagle dogs in a reference formulation (Treatment A) under fed conditions. The reference formulation was an oil-based composition containing a surfactant. Four beagle dogs were used in these studies; all dogs received HPR with at least one week between treatments. The dose of HPR for treatment A and E<sub>1</sub> was 200 mg; it was administered in suspension in treatment A and in solution in Treatment E<sub>1</sub>, and in each case was administered as two 100 mg capsules. In Treatment E<sub>2</sub>, 100 mg of HPR in solution was administered as one 100 mg capsule. All the data for Treatment E<sub>2</sub> are presented with normalization to a 200 mg dose.

Dogs received food and water ad-lib during Treatment A and Treatment E<sub>2</sub>. They were food-fasted for 12 hours before receiving Treatment E<sub>1</sub>; the fasting continued until two hours after dosing.

Plasma samples were analyzed for HPR by a high pressure liquid chromatography procedure. Plasma concentration of HPR in this study are summarized in Table 4 and Figure 2.

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Mean peak HPR concentrations were 1660, 4238 and 8174 ng/ml for Treatment A, E<sub>1</sub> and E<sub>2</sub>, respectively (Table 4). The mean area under the curve, AUC (0-80 hr) values were 22666, 62590 and 95935 ng.hr/ml for Treatment A, E<sub>1</sub> and E<sub>2</sub>, respectively (Table 5). It is readily apparent that the bioavailability of HPR administered in Formulation VII (Treatment E<sub>1</sub> and E<sub>2</sub>) was greater than the bioavailability of HPR administered in the reference formulation (Treatment A). Comparison of results obtained when Formulation VII was administered to animals in the fed state (E<sub>1</sub>) with results obtained when the formulation was fed to fasted animals (E<sub>2</sub>) indicates that additional lipids (from foods consumed) resulted in a further increase in AUC (1.5 fold increase between Treatment E<sub>2</sub> and E<sub>1</sub>). The unsaturated lysophosphatidyl cholines are particularly useful for translocation of absorbed fat into the lymph. Since these unsaturated lysophosphatidyl cholines may have been associated with the HPR, there was insufficient 18:1 lysoPC for both solubilization of the HPR and translocation of the absorbed lipids and HPR into the lymph. Consequently, those drugs which interact with the lysophosphatidyl choline in the lipid formulation apparently require a greater mole ratio of lysophosphatidyl choline with respect to fatty acids and monoglycerides.

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Table 4: Summary of Plasma Concentration-Time  
Data of HPR in Four Dogs Following  
the Oral Administration of HPR in  
Formulation VII

5	Formulation State	<u>Mean HPR Concentration In Plasma - ng/ml</u>		
		Reference A Fed	Lipid-E <sub>1</sub> Fasted	Lipid-E <sub>2</sub> <sup>a</sup> Fed
	<u>Time (Hours)</u>	<u>Plasma HPR Concentration (ng/ml)</u>		
	0	.0	24.0	121.9
10	0.5	219.9	238.9	345.5
	1	769.7	1093.3	2388.3
	2	1430.6	3124.7	7259.8
	3	1490.5	3866.0	8032.5
	4	1325.2	4078.8	6841.1
15	5	1105.2	3599.1	5411.0
	6	914.3	3021.3	4386.7
	7	797.3	2740.7	3402.7
	24	187.4	557.5	852.6
	30	198.0	426.5	646.1
20	48	93.9	253.3	449.3
	54	79.4	193.6	333.9
	72	69.7	149.0	276.0
	80	47.8	114.5	210.3

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<sup>a</sup>Corrected to Base Dose of 200 mg.



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Table 5: Area under the Plasma Concentration-Time Curve [AUC (0-80 hr)] of HPR in Four Dogs Following the Oral Administration of HPR in Formulation VII

5	<u>HPR-AUC (mg H/ml)</u>			
	Formulation State	Reference A Fed	Lipid-E <sub>1</sub> Fasted	Lipid-E <sub>2</sub> <sup>a</sup> Fed
	Dog #			
10	1	28609	50044	107106
	2	15964	84898	127589
	3	21190	78476	56274
	4	24900	36941	92721
<hr/>				
	Mean	22666	62590	95935
	S.D.	5398	22842	30054
15	Median	23045	64260	99939
	G Mean	22156	59241	91905
<hr/>				
As a % of A				
20	Mean		276	423
	Median		279	434
	G Mean		267	415

<sup>a</sup>Corrected to a base dose of 200 mg.

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Industrial Applicability

The composition of this invention has industrial applicability in the delivery of orally administered drugs or other substances. It can also  
5 serve as a readily absorbed source of energy from fat.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such  
10 equivalents are intended to be encompassed by the following claims.

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CLAIMS

1. A composition, comprising:
  - a. at least one non-esterified fatty acid having 14-18 carbon atoms;
  - 5 b. at least one monoglyceride which is a monoester of glycerol and a fatty acid having 14-18 carbon atoms;
  - c. lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms; and
  - 10 d. a drug.
  
2. A composition for increasing absorption of a drug and for increasing transport of non-esterified fatty acids and monoglycerides in  
15 the lymphatics of an individual, comprising:
  - a. non-esterified fatty acids having 14-18 carbon atoms;
  - b. monoglycerides which are monoesters of glycerol and a fatty acid having 14-18  
20 carbon atoms;
  - c. lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms; and
  - d. a drug,  
25 the lysophosphatidyl choline being present in the composition in an amount sufficient for solubilization of said drug in the composition and for increasing uptake of said fatty acids and said monoglycerides  
30 into the lymphatics of the individual.

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3. A composition, comprising:
- a. at least one non-esterified fatty acid having 14-18 carbon atoms and at least one monoglyceride which is a monoester of glycerol and a fatty acid having 14-18 carbon atoms, said fatty acid and said monoglyceride comprising from about 70.0 mole percent to about 99.0 mole percent of the composition and being present in the composition in a molar ratio of between about 1:2 and about 2:1;
  - b. lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms, said lysophosphatidyl choline comprising from about 1.0 mole percent to about 30.0 mole percent of the composition; and
  - c. a drug.
4. A composition of Claim 3 in which the molar ratio of fatty acid:monoglyceride is about 2:1 and lysophosphatidyl choline comprises from about 3.0 mole percent to about 13.0 mole percent.
5. A lipid composition of Claim 3 having non-esterified saturated fatty acids having 14-18 carbon atoms and a sufficient quantity of calcium ions to form a salt with the non-esterified saturated fatty acids.

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## 6. A composition, comprising:

- 5           a. at least one non-esterified fatty acid selected from the group consisting of: palmitoleic, oleic, linoleic, linolenic and saturated fatty acids having 14-18 carbon atoms;
- 10           b. at least one monoglyceride which is a monoester of glycerol and a fatty acid selected from the group consisting of: palmitoleic, oleic, linoleic, linolenic and saturated fatty acids having 14-18 carbon atoms;
- 15           c. lysophosphatidyl choline having as the fatty acid moiety a fatty acid selected from the group consisting of: palmitoleic, oleic, linoleic, linolenic and saturated fatty acids having 14-18 carbon atoms; and
- 20           d. a drug,
- 25           the fatty acid and the monoglyceride together comprising from about 70.0 mole percent to about 99.0 mole percent of the composition and being present in a ratio of fatty acid:monoglyceride of between about 1:2 and about 2:1 and the lysophosphatidyl choline comprising from about 1.0 mole percent to about 30.0 mole percent of
- 30           the composition.

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7. A composition, comprising:
- a. non-esterified fatty acids having 14-18 carbon atoms;
  - b. monoglycerides which are monoesters of glycerol and a fatty acid having 14-18 carbon atoms;
  - c. lysophosphatidyl choline having a fatty acid with 14-18 carbon atoms as its fatty acid moiety; and
  - d. a drug,
- the non-esterified fatty acids and the monoglyceride comprising about 87.0 to 97.0 mole percent of the composition and being present in a fatty acid:monoglyceride molar ratio of about 2:1 and the lysophosphatidyl choline comprising from about 3.0 mole percent to about 13.0 mole percent of the composition.
8. The lipid composition of Claim 7 in which the drug is a fat-soluble vitamin.
9. The composition of Claim 7, in which the non-esterified fatty acid, the fatty acid of the monoglyceride and the fatty acid of the lysophosphatidyl choline are selected from the group consisting of: palmitoleic, oleic, linoleic, linolenic, myristic, palmitic and stearic.

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10. The composition of Claim 7 in which the non-esterified fatty acid is oleic acid; the monoglyceride is mono-olein or mono-palmitin and the lysophosphatidyl choline is selected from the group consisting of: lysophosphatidyl choline derived from soy lecithin, myristoyl lysophosphatidyl choline, palmitoyl lysophosphatidyl choline, and oleoyl phosphatidyl choline.
- 10 11. A composition, comprising:
- a. oleic acid and mono-olein in a molar ratio of about 2:1;
  - b. about 3.0 mole percent lysophosphatidyl choline; and
  - 15 c. vitamin A.
12. In the co-administration of a vehicle and a drug, the improvement whereby the vehicle is a composition comprised of:
- 20 a. at least one non-esterified fatty acid having 14-18 carbon atoms and at least one monoglyceride which is a monoester of glycerol and a fatty acid having 14-18 carbon atoms, said non-esterified fatty acid and said monoglyceride being present
  - 25 in the composition in a molar ratio of between about 1:2 and about 2:1; and
  - b. lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms, said lysophosphatidyl choline comprising
  - 30 from about 1.0 mole percent to about 30.0 mole percent of the composition.

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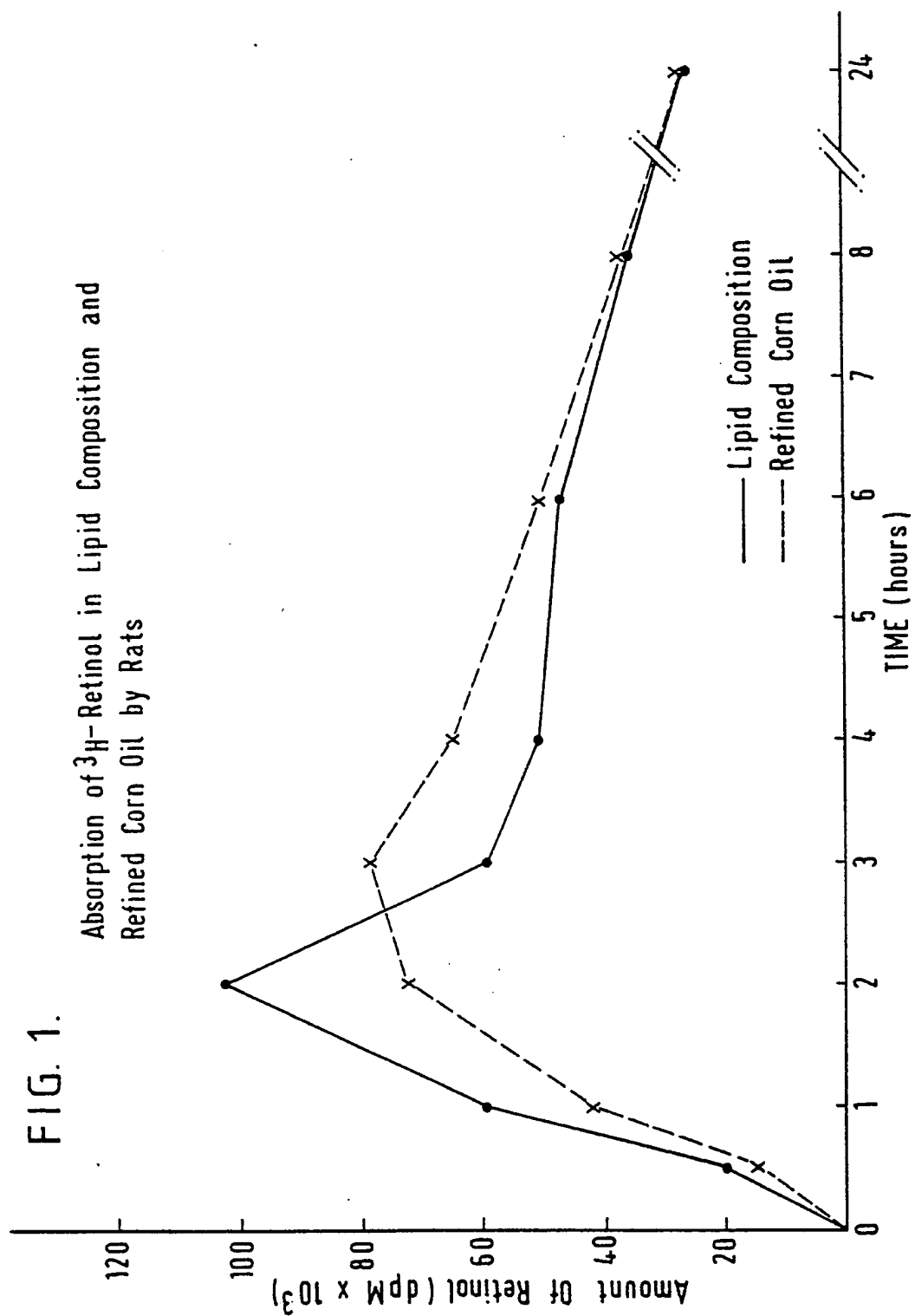
13. A method of delivering vitamin A comprising the co-administration of:
- a. vitamin A and
  - b. a composition comprised of:
    - 5 1. at least one non-esterified fatty acid having 14-18 carbon atoms and at least one monoglyceride which is a monoester of glycerol and a fatty acid having 14-18 carbon atoms, said  
10 non-esterified fatty acid and said monoglyceride being present in the composition in a molar ratio of between about 1:2 and about 2:1; and
    - 15 2. lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms, said lysophosphatidyl choline comprising from about 1.0 mole percent to about 30.0 mole percent of the composition.
- 20 14. A method of delivering a readily absorbable source of calories derived from fat, comprising the oral administration of a lipid composition comprised of:
- 25 a. non-esterified fatty acids having 14-18 carbon atoms and monoglycerides which are monoesters of glycerol and a fatty acid having 14-18 carbon atoms, said fatty acids and said monoglyceride comprising from about  
30 70.0 mole percent to about 99.0 mole



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- percent of the lipid composition and being present in a molar ratio of between about 1:2 and about 2:1 and
- b. lysophosphatidyl choline in which the fatty acid moiety has 14-18 carbon atoms, said lysophosphatidyl choline comprising from about 1.0 mole percent to about 30.0 mole percent of the lipid composition.

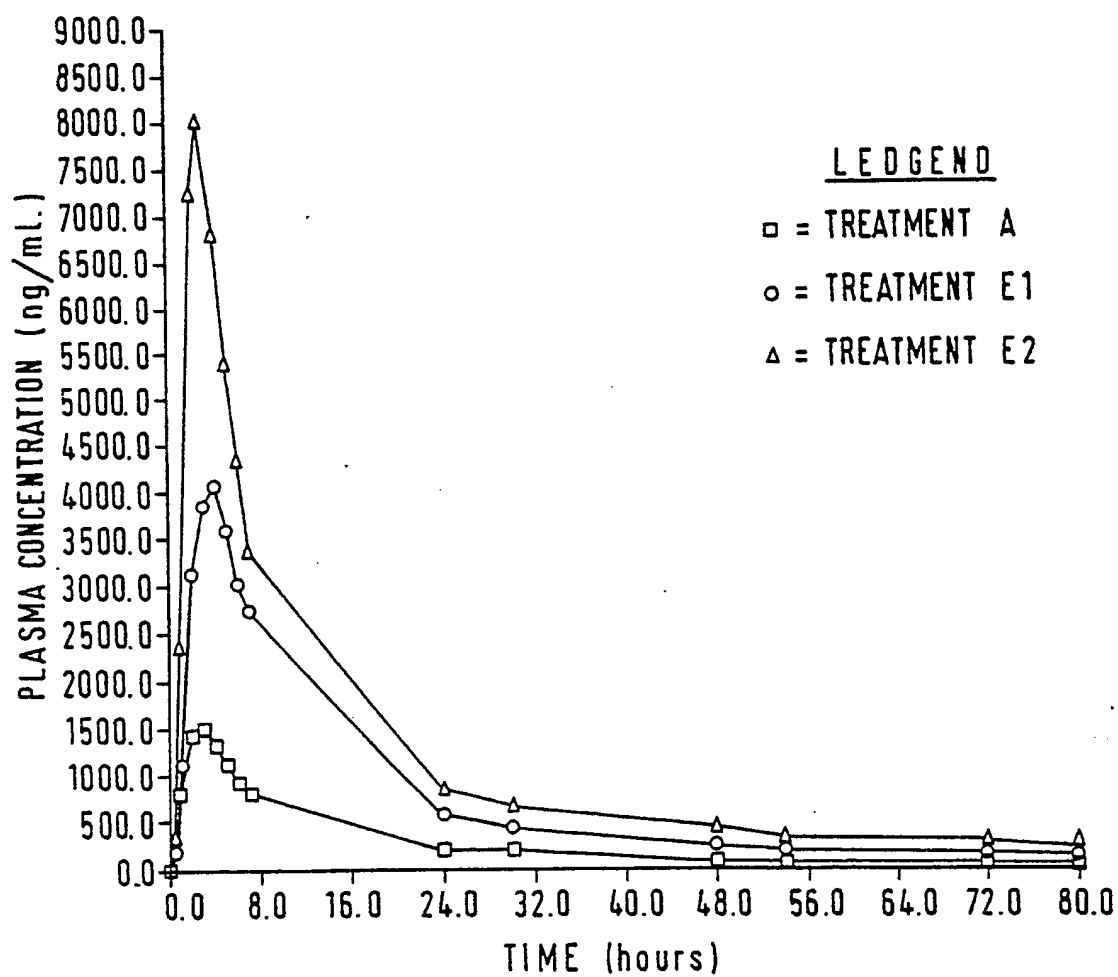
1/2



SUBSTITUTE SHEET

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FIG. 2.



<sup>a</sup>Data for Treatment E2 are normalized to a 200 mg dose.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 86/00637

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC 4 A 61 K 47/00 IPC:		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC <sup>4</sup>	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X, Y	DE, C, 286061 (ERBEN DES KARL ALFRED FISCHER) 2 February 1913, see page 1, lines 60-70 --	1-13
Y	FR, A, 2427100 (KALI-CHEMIE PHARMA GMBH) 28 December 1979, see page 10, line 1 - page 11, line 5; claims 1-10 --	1-13
A	EP, A, 0023349 (EISAI CO. LTD.) 4 February 1981, see page 16, lines 1-20; claims 1-5 --	1-13
A	WO, A, 83/00294 (ARTHUR D. LITTLE, INC.) 3 February 1983 (cited in the application)  -----	1-13
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Δ" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
31st July 1986	22 AUG 1986	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	M. VAN MOL	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 86/00637 (SA 12950)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/08/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-C- 286061		None	
FR-A- 2427100	28/12/79	None	
EP-A- 0023349	04/02/81	JP-A- 56018914 CA-A- 1159767	23/02/81 03/01/84
WO-A- 8300294	03/02/83	EP-A- 0084052	27/07/83

For more details about this annex :  
see Official Journal of the European Patent Office, No. 12/82